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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/590,936	08/28/2006	Rita De Santis	725.1051	2737

20311 7590 11/17/2010

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EXAMINER	
HADDAD, MAHER M	

ART UNIT	PAPER NUMBER
1644	

NOTIFICATION DATE	DELIVERY MODE
11/17/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

info@lmiplaw.com

Office Action Summary	Application No.	Applicant(s)	
	10/590,936	DE SANTIS ET AL.	
	Examiner	Art Unit	
	Maher M. Haddad	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 October 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-34* is/are pending in the application.

4a) Of the above claim(s) *9-11,13,14,17-20,29, 31-32 and 34* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8,12,15,16,21-28,30 and 33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *08/28/2006 and 02/26/2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-34 are pending.

Upon reconsideration the Examiner rejoin Group V with Group I.

2. Applicant's election with traverse of Group I, claims 1-8, 12, 15-16, 21-28 and 33, now claims 1-8, 12, 15-16, 21-28, 30 and 33 directed to an anti-human tenascin a monoclonal antibody, preferably murine, whose light and heavy chain variable region sequences are SEQ ID 1 and SEQ ID 2, respectively, its proteolytic fragments capable of binding to an antigenic epitope within the A(I.4)-D region of human tenascin, its recombinant derivatives, its conjugates and similar functional analogues capable of binding to an antigenic epitope within the A(1-4)-D region of human tenascin, fragments, recombinant derivatives, derivatives, bioltinylated, hybridoma, pharmaceutical compositions and kits thereof and the species of ST2210, filed on 10/25/2010, is acknowledged.

Applicant's traversal is on the grounds that a search for the subject matter of the group selected will of necessity also involved a search for the subject matter of Groups II-VII, since it is in fact Group I anti- human tenascin monoclonal antibody which is encoded by the Group II, comprises the Group III, is used in Group IV, is contained in Group V and is used in Groups VI and VII. Similarly, once the invention of Group I has been searched, the subject matter in the remaining groups will not be an undue burden for the Examiner and it would be efficient to consider all pending claims at this time. In addition, the Examiner has the discretion to prosecute all of the pending claims in a single patent application. In fact, "[I]fthe search and examination of an entire application can be made without serious burden, the examiner must examine it on the merits, even though it includes claims to independent and distinct invention." (Emphasis added, MPEP § 803, second paragraph). Further, Applicants urge that also the species recited in claims 22-26 be examined together. A search for the subject matter of the species selected will of necessity involve a search for the subject matter of the other species as well. Once the species selected are searched, the subject matter in the additional species will not be an undue burden for the examiner since the anti-human tenascin antibodies, or their proteolytic fragments, or recombinant derivatives conjugated or analogues all share the same main chemical structure. Similarly, all of the biotin DOTA also share the same main chemical structure. Thus, it would be efficient to consider all of the species at this time.

This is not found persuasive because Applicant's inventions do not contribute a special technical feature when viewed over the prior art of WO 03/072608.

The `608 publication teaches and claims tenascin-specific antibody preferentially directed towards the A-D fragment (see published claim 31). The `608 publication teaches a therapeutic kit, a biotinylated antibody is combined with other tenascin-specific antibodies preferentially

directed towards the A-D fragment. Alternatively, the biotinylated antibody is combined with other tumor specific antibodies (see page 13, 3rd ¶). The reference antibodies are considered to have similar functional analogues capable of binding to an antigenic epitope within the $A_{(1-4)}$-D region of human tenascin.

Accordingly, Applicant's inventions do not have a single general inventive concept and so lack unity of invention as set forth in this Office Action (see the rejection under 102 below).

The requirement is still deemed proper and is therefore made FINAL.

3. Claims 9-11, 13-14, 17-20, 29, 31-32 and 34 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to nonelected inventions.

4. Claims 1-8, 12, 15-16, 21-28, 30 and 33 are under examination as they read on an anti-human tenascin a monoclonal antibody, preferably murine, whose light and heavy chain variable region sequences are SEQ ID 1 and SEQ ID 2, respectively, its proteolytic fragments capable of binding to an antigenic epitope within the A(I.4)-D region of human tenascin, its recombinant derivatives, its conjugates and similar functional analogues capable of binding to an antigenic epitope within the A(1-4)-D region of human tenascin, fragments, recombinant derivatives, derivatives, bioltinylated, hybridoma, pharmaceutical compositions and kits thereof and the species of ST2210 and a process for preparation and a method of for the preparation of a pharmaceutical product.

5. Applicant's IDS, filed 08/28/2006 and 02/26/2008, is acknowledged, however, the IDS filed 02/26/2008 was crossed out because it is duplicate of the IDS filed 08/28/2006.

6. The specification on page 5, lines 6-7; page 10, lines 5-10 and line 13; page 11, last ¶ and page 24, top ¶, is objected to because it disclsoes that "SEQ ID NO: 3" is nucleic acid not amino acid sequence and SEQ ID NO: 3 is VH not VL. "SEQ ID NO: 2" is VL not VH and amino acid sequence not nucleic acid sequence. On page 11 last ¶, SEQ ID NO: 2 is amino acid sequence not NA sequence. On page 24, top ¶, SEQ ID NO: 2 is amino acid sequence and VL sequence not VH. Correction is required.

7. It is suggested the term "an isolated anti-human tenscin ..." be cited in the preamble of the claim 1. Further, for clarity reasons, it is suggested that "protein" claim 12 be change to "an isolated antibody".

8. Claim 1 is objected to because the sequence identification number should be referred to as "SEQ ID NO:" not "SEQ ID". See MPEP 2422.03.

9. The use of a pronoun "its" in claims 1, 3, 17, 21-23, 27-28 and 30, is objected, it is suggested to replace the pronoun by what is intended by "it".

10. Claims 1 and claims dependent thereof are improperly recites the plural form of "fragments", "derivatives", "fragments analogues", "conjugates", "markers", "agents", "antibodies" and "compositions". It is suggested that the claim recite the singular form. Further, the claims are missing an article such as "A" or "The" before the preamble of the claims.

11. Claims 15 are objected to for the following informalities: claim 15 recites "with the number PD03003", it appears that the claims are missing the word accession. It is suggested that the claims changed to recite "with the accession number PD03003".

12. Claim 24 is objected to because formula (I) and formula (II) insertion does not correspond to the correct location of the (I) and (II). The formulas are inserted before the formula is referred to in the claim. The formulas should be inserted after (I) and (II) is mention in the claim.

13. The following is a quotation of the second paragraph of 35 U.S.C. 112.

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

14. Claims 1-8, 12, 15-16, 21-28, 30 and 33 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

I. Claims 1-8, 12, 15-16, 21-28, 30 and 33 are generally narrative and indefinite, failing to conform with current U.S. practice. They appear to be a literal translation into English from a foreign document and are replete with grammatical and idiomatic errors.

II. The term "preferably murine" in claim 1 is indefinite because the narrow range within the broad range using the term "preferably" renders the claim indefinite.

III. The preamble of the claim 1 recites "anti-human tenascin monoclonal antibody "i.e., protein", however, the cited VL sequence "SEQ ID 1" is nucleic acid sequence and is limited to its nucliec acids componants. Furthermore, the cited VH sequence "SEQ ID 2" is not VH, it is VL amino acid sequence. Accordingly, claim 1 is indefinite. Applicants have failed to point out how a nucleic acid would comprise an amino acid sequence and how VL becomes VH.

IV. The recitation "protein coded by the nucleic acid sequences .... SEQ ID 2" in claim 12 is indefinite because "SEQ ID 2" is an amino acid sequence and is limited to its amino acid components.

V. The "biotinylated antibody" recited in claim 8, lacks sufficient antecedent basis in base claim one. Base claim 1 recites only "recombinant derivatives, its conjugates and similar functional analogues".

VI. The recitation "as defined above" in claim 8 is ambiguous, it is unclear in which "above" claim(s) the biotinylated derivatives are defined. There are 7 claims preceding claim 8.

VII. Claim 16 is indefinite because the method of production recited would not produce the "recombinant derivatives" and "conjugates" antibody of claim 1.

VIII. The recitation "a three-step pre-targeting radioimmunotherapy" in claim 22 is indefinite because it is unclear what three-step pre-targeting radioimmunotherapy is contemplated.

IX. The recitation "whole numbers from 0 to n" in claim 24 is indefinite. It is not clear what whole number defends "n". Is n equals 1, 4, 10, 20 or more?

X. Did Applicant intend to write 'disuccinimidyl' before 'suberate' in claim 25.

15. The following is a quotation of the first paragraph of 35 U.S.C. 112:
The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

16. Claim 15 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

It is apparent that the hybridoma that producing the antibody deposited under deposit number PD03003, i.e., ST2485 antibody, is required to practice the claimed invention. As a required element, it must be known and readily available to the public or obtainable by a repeatable method set forth in the specification. If it is not so obtainable or available, the enablement requirements of 35 USC 112, a deposit of the hybridoma, which produces this antibody, may satisfy first paragraph. See 37 CFR 1.801-1.809.

It is noted that the specification on page 5, 4th ¶, discloses that the hybridoma cell line was deposited at the centro di Biotecnolgie Avanzate, Largo Rossana Benzi 10, Genoa, Italy, on 12 November 2003 in accordance with the provisions of the Budapest Treaty, under deposit number PD03003.

However, the following requirements must still be met in order to fulfill the requirements of 37 CFR 1.801-1.809 (see also MPEP 2402-2411).

a) indicates that the deposit was made under the terms of the Budapest Treaty (see 37 CFR 1.806 and MPEP 2408) or otherwise fulfills the requirements of 37 CFR 1.801-1.809;

b) assure that all restrictions imposed by the depositor and the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent in U.S. patent applications (see 37 CFR 1.808 (a)(2) and MPEP 2410-2410.01);

c) promptly submit a verified statement form a person in a position to corroborate the fact, that the biological material which is deposited is the biological material specifically identified in the application as filed, except if the person is an attorney or agent registered to practice before the Office, in which the case the statement need not be verified (see MPEP 1.804(b) and MPEP 2406).

In the instant case applicant has not fulfill part (b) and (c) of the requirements. Applicant's attention is directed to In re Lundak, 773 F.2d. 1216, 227 USPQ 90 (CFC 1985) and 37 CFR 1.801-2.809 for further information concerning deposit practice.

15. Claims 1-8, 12, 16, 21-28, 30 and 33 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant is in possession of an isolated monoclonal antibody anti-human tenascin comprising the light chain variable region of SEQ ID NO: 2 and heavy chain variable region sequence of SEQ ID NO:4, or the proteolytic fragments thereof which binds to an antigenic epitope within the $A_{(1-4)}$-D region of human tenascin, a conjugate thereof comprising the antibody or fragment thereof and a marker or a diagnostic agent, a chimeric antibody thereof, a biotinylated antibody or fragment thereof, the hybridoma cell line producing the antibody, a process for the preparation of the antibody, a kit, container or composition comprising the antibody or fragment thereof.

Applicant is not in possession of any "recombinant derivatives, its conjugates and similar functional analogues" of the antibody and the fragments thereof in claims 1, 21, 22, 23, 27, 28, 30 and 33, in which the murine constant region is replaced by a "biologically active component" in claim 4, in which the murine constant region is replaced by a "pharmacologically active component" in claim 5, in which the murine constant region is replaced by a "member of the avidin family" in claim 6, conjugated with "biologically active substances" in claim 7, biotinylated derivatives in claim 8 and protein coded for by the nucleitide sequences SEQ ID NO: 1 and SEQ ID NO:3 or "its fragments".

Applicant has disclosed only ST2485 antibody comprising the heavy and light chain of SEQ ID NO: 2 and 4, fragment thereof, a conjugate, a recombinant and a biotinylated antibody of

fragment thereof, a kit, a container or a composition comprising said antibody or fragment thereof; therefore, the skilled artisan cannot envision all the contemplated antibody derivatives including recombinant derivatives, conjugates and functional analogues, in which murine constant region is replaced by a biologically/pharmacologically active component. Consequently, conception cannot be achieved until a representative description of the structural and functional properties of the claimed invention has occurred, regardless of the complexity or simplicity of the method. Adequate written description requires more than a mere statement that it is part of the invention. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC1993). The Guidelines for the Examination of Patent Application Under the 35 U.S.C.112, ¶1"Written Description" Requirement make clear that the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species disclosure of relevant, identifying characteristics, i.e., structure or other physical and or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus (Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 20001, see especially page 1106 3rd column).

The specification on page 10, under Detailed description of the invention, discloses that recombinant derivatives preferred are those in which the murine constant region is replaced by its human counterparts, or by a biologically or pharmacologically active component or by a member of the avidin family (see ¶7). Further the specification discloses that the conjugated derivatives are those in which a biologically active potion is bound to the antibody (see page 11, ¶1). However, the claims read on a genus of antibodies including variants of the antibodies. The claimed derivatives (e.g., variants) can have amino acid substitutions, deletions, insertions, or additions, as compared to SEQ ID NOS: 2 and 4. The specification does not provide an actual reduction to practice of any variants of the antibody. The specification does not describe the complete structure or physical or chemical properties of any variants of the anti-human tenascin monoclonal antibody comprising SEQ ID NO: 2 and 4. However, one of ordinary skill would not be able to identify out further testing which of these antibody variants have the activity of binding to tenascin.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.). Consequently, Applicant was not in possession of the instant claimed invention. See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.

Applicant is directed to the final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

14. Claims 1-8, 16, 21-28, 30 and 33 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated monoclonal antibody anti-human tenascin comprising the light chain variable region of SEQ ID NO: 2 and heavy chain variable region sequence of SEQ ID NO:4, or the proteolytic fragments thereof which binds to an antigenic epitope within the $A_{(1-4)}$-D region of human tenascin, a conjugate thereof comprising the antibody or fragment thereof and a marker or a diagnostic agent, a chimeric antibody thereof, a biotinylated antibody or fragment thereof, the hybridoma cell line producing the antibody, a process for the preparation of the antibody, a kit, container or composition comprising the antibody or fragment thereof, does not reasonably provide **enablement** for of any "recombinant derivatives, its conjugates and similar functional analogues" of the antibody and the fragments thereof in claims 1, 21, 22, 23, 27, 28, 30 and 33, in which the murine constant region is replaced by a "biologically active component" in claim 4, in which the murine constant region is replaced by a "pharmacologically active component" in claim 5, in which the murine constant region is replaced by a "member of the avidin family" in claim 6, conjugated with "biologically active substances" in claim 7, biotinylated derivatives in claim 8. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and or use the invention commensurate in scope with this claim.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention.

The specification does not provide a sufficient enabling description of the claimed invention. The specification discloses only a single monoclonal antibody anti-human tenascin comprising the amino acids sequences of the heavy and light chain of SEQ ID NOs: 2 and 4 which is capable of binding to an antigenic epitope within the $A_{(1-4)}$-D region of human tenascin (e.g., page 0, 5th ¶). Further the specification discloses that the anti-human tenascin monoclonal antibodies can be useful in diagnostic and treatment procedures for tumors expressing tenascin (see page 1, 1st ¶). Further, the specification discloses that monoclonal antibodies are the ideal instrument for specifically localizing the tumor and when combined with the avidin/biotin amplification system, constitute and extremely potent method for directing active molecules to the tumor site (see page 1, 3rd ¶). The instant claims encompass in their breadth any antibody, its fragment, recombinant derivatives, or conjugate derivatives, functional analogues and biotinylated derivatives.

In additively study of the two antibodies TS2485 and ST2146 was conducted in vivo in an animal model. The specification discloses the mixture of the two labeled antibodies presents an accumulation in the tumor amounting to 93% of the theoretical value (see page 23, 1st ¶).

After a review of the specification with respect to the nature of antibody "derivatives", the specification was not found to provide sufficient guidance to the skilled artisan as to how to make and use ST2485 "derivatives" commensurate in scope with the instant claims. In

particular, it is noted that the claim 12 recites protein coded for by the nucleotide sequences SEQ ID 1 and SEQ ID 3 or its "fragments" and similar functional analogues capable of binding to and an antigenic epitope within the $A_{(1-4)}$-D region of human tenascin in claim 1. The claims read on a derivative, by way of amino acid substitution, deletion, addition or insertion of the amino acid sequence set out in SEQ ID NO: 2 and 4.

Given the breadth encompassed by the instant claims, Applicant has not provided the skilled artisan with sufficient guidance as to the identity of all residues to be changed, to be left unchanged, to be deleted, or to have additional (unidentified) sequences inserted between. Without clear direction and guidance as to the nature of the changes made to SEQ ID NOS: 2 and 4, the skilled artisan would be faced with undue experimentation to produce the immense number of "analogs" and "recombinant" encompassed by the instant claims and determine if there were any operative embodiment that would result in the binding to human tenascin. Thus the specification does not appear to provide the skilled artisan with sufficient guidance to make and use such "analogs" and "derivatives", commensurate in scope with the claimed invention.

However, the art acknowledges that function cannot be predicted based solely on structural similarity to a protein found in the sequence databases and recognized that it was unpredictable if any functional activity will be shared by two polypeptides having less than 100% identity over the full length of their sequences. Accordingly, it is unpredictable if any functional activity will be shared by two polypeptides having less than 100% identity over the full length of their sequences. The specification does not provide sufficient guidance and working examples, predicting what changes can be made to the amino acid sequence of SEQ ID NO: 2 and 4 that after modification will retain both structure and have similar function as the antibody comprising SEQ ID NO: 2 and 4 is unpredictable. Because of the unpredictability and the lack of guidance, an undue experimentation would be required to determine which modifications would be acceptable to retain occluding structural and functional activity, and the fact that the relationship between the sequence of a protein/peptide and its tertiary structure (i.e. its activity) are not well understood and are not predictable. The state of prior art teaches that event a single amino acid substitution or what appears to be an inconsequential chemical modification will often dramatically affect the biological activity and characteristic of a protein/peptide. No analogs, derivatives, etc. have been provided, and the claims cannot be considered enabled for anything other than that antibody that comprises both SEQ ID NO:2 and 4.

Reasonable correlation must exist between the scope of the claims and scope of the enablement set forth. In view on the quantity of experimentation necessary the limited working examples, the nature of the invention, the state of the prior art, the unpredictability of the art and the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

15. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

16. Claims 1-8, 16, 21-23, 27-28, 30 and 33 are rejected under 35 U.S.C. 102(b) as being anticipated by WO 03/072608.

The `608 publication teaches and claims tenascin-specific antibody preferentially directed towards the A-D fragment (see published claim 31). The `608 publication teaches a therapeutic kit, a biotinylated antibody is combined with other tenascin-specific antibodies preferentially directed towards the A-D fragment. Alternatively, the biotinylated antibody is combined with other tumor specific antibodies (see page 13, 3rd ¶). The `608 publication teaches antibody fragments which may also contain additional markers and diagnostic agents (see page 4, 1st ¶). Further, the `608 publication teaches recombinant derivatives are those where the murine constant region is replaced by the human counterpart or those where the murine constant region is replaced by a biologically active moiety, such as, for example, a member of the avidin family or those wherein the murine constant region is replaced by a pharmacologically active moiety (see page 10, 5th ¶). The `608 publication teaches that monoclonal antibody or proteolytic fragments or derivatives thereof are biotinylated, in a more particularly preferred embodiment, the medicament is suitable for radioimmunotherapy, in particular for carrying out the three-step pre-targeting method, as described in the art. The `608 publication teaches kits being composed of 5 vials, whose first vial contains the biotynilated antibody or fragment or derivative thereof; the second vial contains an avidin, the third vial contains biotinylated albumin, the fourth vial contains a streptavidin, the fifth vial contains radiolabelled biotin or biotin derivative (see pp. 12, 2nd ¶). The `608 publication teaches a method to generate a new hybridoma cell clone with the specificity of BC4 but lacking the expression of non functional light chain. The schematic representation of human tenascin-C, the related recombinant antigenic fragments and reagents. pTn28 immunized splenocytes were fused to Sp2/0Agl4 non producing myeloma cells by standard method and the hybridoma population screened by ELISA on SK-MEL-28 (human melanoma cell line) purified tenascin (see Example 1). The `608 publication teaches compositions containing these antibodies and antibody fragments, and diagnostic and therapeutic compositions containing them, their use in therapy and diagnostics and methods of making these antibody and antibody fragments (see page 4, 1st ¶). The 608 publication teaches that the biotinylated antibody which binds to EGF-like repeat region of human tenascin is combined with other tenascin-specific antibodies preferentially directed towards the A-D fragment (see page 13, 2nd ¶). Finally, the 608 publication teaches a container, optionally containing multiple compartments, comprising the biotinylated antibody or fragments or derivatives thereof, buffers and reagents suitable for use in a therapeutic kit for a three-step pre-targeting method (see pp. 13, 3rd ¶). The reference antibodies are considered to have similar functional analogues capable of binding to an antigenic epitope within the $A_{(1-4)}$-D region of human tenascin.

The reference teachings anticipate the claimed invention.

17. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

18. Claims 1-8, 16, 21-28, 30 and 33 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 03/072608 in view of Pat. 7,390,828 and US. Pat. 7,425,317.

The teachings of `608 publication have been discussed, supra.

The claimed invention differs from the reference teachings only by the recitation of biotin DOTA is the formula (I) compound comprising hydrogen or formula II in claims 22 and 24 and an avidin dimmer in which two avidin molecules are bound via the –NH2 groups by means of suberate in claim 25 and an avidin dimmer in which two molecules are bound via the COOH groups by means of polythylene glycol with a molecular weight of 3,400 in claim 26.

However, the `828 patent teaches and claims formula (I) compounds and processes for their preparation, and their uses for the preparation of conjugates with radionuclides for use in human and animal therapy and diagnostics, particularly for the diagnosis and therapy of pathological conditions such as tumours (see patented claims 1-2). The `828 patent teaches that the formula (I) compound presents the advantage of not undergoing metabolic reactions capable of releasing the complexing part of the molecule. In this way, the molecule will be completely eliminated by the body in unaltered form, thus avoiding the problem of the possible release of the chelating part, containing the metal ions imprisoned within it (see col., 2, lines 25-35).

The `317 patent teaches and claims a kit for radiotherapy or diagnosis of tumours, comprising a biotinylated anti-tenascin antibody and an avidin dimer, in which two molecules of avidin are bound via --NH.sub.2 groups by crosslinking with disuccinimidyl suberate. A kit for radiotherapy or diagnosis of tumours, comprising a biotinylated anti-tenascin antibody and an avidin dimer, in which two molecules of avidin are bound via --COOH groups by crosslinking with polyethylene glycol diamine with a molecular weight of 3400. The `317 patent teaches that avidin dimers effective in increasing the concentration of radioactive biotin in pretargeted radioimmunotherapy.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the biotin taught by the `608 publication with biotin DOTA taught by `828 patent for the advantage of not undergoing metabolic reactions capable of releasing the complexing part of the molecule. In this way, the molecule will be completely eliminated by the body in unaltered form, thus avoiding the problem of the possible release of the chelating part, containing the metal ions imprisoned within it.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the avidin taught by the `608 publication with avidin dimers taught by `317 patent for the advantage of increasing the concentration of radioactive biotin in pretargeted radioimmunotheray.

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

19. No claim is allowed.

20. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maher Haddad whose telephone number is (571) 272-0845. The examiner can normally be reached Monday through Friday from 7:30 am to 4:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

November 11, 2010

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